REMARKS/ARGUMENTS

Upon entry of this amendment, claims 1-16 and 19 are pending in this application and are presented for examination. Claims 17, 18, and 20-46 have been withdrawn from consideration by the Examiner as being directed to a non-elected invention. Claims 1, 4, 5, 7, 8, and 12 have been amended. Claim 47 has been newly added. No new matter has been introduced with the foregoing amendments. Reconsideration is respectfully requested.

I. FORMALITIES

The amended claims find support throughout the specification as filed. In particular, support for amended claim 1 and new claim 47 is found, for example, on page 9, lines 5-22. Support for amended claims 4 and 5 is found, for example, on page 10, lines 12-19. Claim 12 has been amended to establish proper dependency from claim 8. Thus, no new matter has been introduced. As such, Applicants respectfully request that the amendments to the claims be entered.

II. INFORMATION DISCLOSURE STATEMENT

In the Office Action, the Examiner alleges that no Information Disclosure Statement (IDS) has been filed in the instant application (*see,* page 4 of the Office Action). However, Applicants respectfully point out to the Examiner that an IDS was submitted on May 23, 2002. A copy of the IDS is attached for the Examiner's convenience as Exhibit A. As such, contrary to the Examiner's allegation, Applicants have filed an IDS in the instant application.

III. SPECIFICATION OBJECTION

The specification has been objected to because the sequences listed in Figures 7, 8, and 13 do not have sequencer identifiers (SEQ ID NOs). However, Applicants respectfully point out to the Examiner that SEQ ID NOs were included for the sequences listed in Figures 7 and 13A in the Preliminary Amendment filed on April 18, 2002. A copy of the Preliminary Amendment is attached for the Examiner's convenience as Exhibit B. Applicants have amended the description to Figure 8 to include SEQ ID NOs for the sequences listed in the figure. As

such, Applicants respectfully request that the Examiner withdraw the objection to the specification.

IV. CLAIM OBJECTION

Claim 1 was objected to because step (ii) does not recite determining the functional effect of the compound upon the TRAC1 polypeptide "or a fragment thereof." In order to expedite prosecution of the present case, Applicants have amended claim 1 to delete the term "fragment thereof" from step (i), thereby rendering the objection moot. As such, Applicants respectfully request that the Examiner withdraw the objection to claim 1.

V. REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 1-16 and 19 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. To the extent the rejection is applicable to the amended set of claims, Applicants respectfully traverse the rejection.

In the Office Action, the Examiner alleges that the term "functional effect" in claim 1 is unclear (*see,* page 5 of the Office Action). The Examiner also alleges that claims 3, 4, 7, 8, and 12 are indefinite because it is unclear when a "functional effect" is a "chemical effect" and when it is a "physical effect" (*see,* page 6 of the Office Action). In response, Applicants assert that the terms "functional effect," "chemical effect," and "physical effect" are clearly defined by the specification as filed. For example, the paragraph on page 10, lines 12-29, and the paragraph bridging pages 10-11 state:

> The phrase "functional effects" in the context of assays for testing compounds that modulate activity of a TRAC1 protein includes the determination of a parameter that is indirectly or directly under the influence of TRAC1, e.g., an indirect, chemical or phenotypic effect such as inhibition of T lymphocyte activation represented by a change in expression of a cell surface marker or cytokine production upon TCR stimulation, or changes in cellular proliferation or apoptosis, ligase activity (ubiquitin ligase activity or ubiquitin-like ligase activity), or TCR signal transduction leading to increases in intracellular calcium or calcium influx; or, e.g., a direct, physical effect such as ligand/substrate binding or inhibition of ligand/substrate binding to TRAC1 (e.g., binding of E2 ubiquitin conjugating enzymes such as UbcH5, 7, and 8) or a TRAC1 domain such as the ring finger or ligase domain. A functional effect therefore includes ligand/substrate binding activity, the ability of cells to proliferate, apoptosis, gene

> expression in cells undergoing activation, ligase activity (ubiquitin ligase activity or ubiquitin-like ligase activity), expression of cell surface molecules such as CD69, TCR signal transduction, including downstream effectors such as second messengers, intracellular calcium release and calcium influx, production of cytokines, and other characteristics of activated lymphocytes. "Functional effects" include *in vitro*, *in vivo*, and *ex vivo* activities.
>
> By "determining the functional effect" is meant assaying for a compound that increases or decreases a parameter that is indirectly or directly under the influence of TRAC1 protein, e.g., measuring physical and chemical or phenotypic effects. Such functional effects can be measured by any means known to those skilled in the art, e.g., changes in spectroscopic (e.g., fluorescence, absorbance, refractive index), hydrodynamic (e.g., shape), chromatographic, or solubility properties for the protein; measuring inducible markers or transcriptional activation of the protein; measuring binding activity or binding assays, e.g. binding to antibodies; measuring changes in ligand binding affinity, either naturally occurring or synthetic; measuring cellular proliferation; measuring apoptosis; measuring cell surface marker expression, e.g., CD69; measuring cytokine; measurement of changes in protein levels for TRAC1-associated sequences; measurement of RNA stability; phosphorylation or dephosphorylation; ligase activity; TCR signal transduction and downstream effectors, e.g., receptor-ligand interactions, second messenger concentrations (e.g., cAMP, IP3, or intracellular Ca^{2+}); calcium influx; identification of downstream or reporter gene expression (CAT, luciferase, β-gal, GFP and the like), e.g., via chemiluminescence, fluorescence, colorimetric reactions, antibody binding, inducible markers, and ligand binding assays.

Applicants submit that this description allows a person of ordinary skill in the art to recognize, without any ambiguity, that a "functional effect" refers to changes in any parameter that is indirectly (*e.g.*, chemical or phenotypic effect) or directly (*e.g.*, physical effect) under the influence of the TRAC1 protein. By providing examples of such parameters and assays for measuring such parameters, the instant specification allows the artisan to appreciate that a "chemical effect" refers to changes in expression of a cell surface marker or cytokine production upon TCR stimulation, cellular proliferation or apoptosis, ligase activity, or TCR signal transduction, whereas a "physical effect" refers to changes in ligand/substrate binding to TRAC1 or a TRAC1 domain such as the ring finger or ligase domain. As a result, an artisan who has read the instant specification would know precisely what constitutes a "functional effect," a "chemical effect," or a "physical effect."

In view of the foregoing remarks, Applicants respectfully request that the Examiner withdraw the rejection under 35 U.S.C. § 112, second paragraph.

VI. REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

A. Written description

Claims 1-16 and 19 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly lacking written description. The Examiner alleges that the phrase "TRAC1 polypeptide or a fragment thereof" reads on an extremely large genus of polypeptides and fragments thereof with no functional limitations and virtually no structural limitations (*see,* pages 6-7 of the Office Action). To the extent the rejection is applicable to the amended set of claims, Applicants respectfully traverse the rejection.

In order to expedite prosecution, Applicants have amended the claims to recite a method for identifying a compound that modulates T lymphocyte activation by contacting the compound with a TRAC1 polypeptide comprising an amino acid sequence having at least about 90% identity to SEQ ID NO:1.

Applicants assert that the amended claims fully comply with the requirements for written description of a chemical genus as set forth in *University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997). As described by the Federal Circuit in *Lilly*, "[a] description of a genus . . . may be achieved by means of . . . a recitation of structural features common to the members of the genus . . . ." *Lilly*, 43 USPQ2d at 1406. Furthermore, the court in *Fiers v. Revel* stated that an adequate written description "requires a precise definition, such as by structure, formula, chemical name, or physical properties." *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). The amended claims set forth both functional elements as well as structural elements, *i.e.,* reference sequences to which members of the claimed genus have a specified percent identity. As a result, the claimed sequences are thereby defined via shared physical and structural properties.

The present invention relates to the discovery that TRAC1 is involved in T cell activation. The genus of TRAC1 polypeptides is claimed by reference to shared structural

features, *i.e.,* amino acid sequences that have at least 90% identity to a reference TRAC1 sequence.

The percent identity of a polypeptide to a reference sequence is a structural feature, as it relies entirely on the sequence of the molecule. In the instant specification, Applicants have provided both reference amino acid sequences as well as sequence analysis algorithms. As required by the standard set forth in *Lilly*, these structural features are common to all of the members of the TRAC1 polypeptide genus. In fact, the specified percent identity to reference sequences for the claimed genus "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (*quoting Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 111, 1116 (Fed. Cir. 1991)). Therefore, Applicants believe that the instant specification appropriately describes the claimed TRAC1 polypeptide genus using structural/physical features, as required by the court in *University of California v. Eli Lilly*.

In view of the foregoing remarks, Applicants respectfully request that the Examiner withdraw the written description rejection under 35 U.S.C. § 112, first paragraph.

B. Enablement

Claims 1-16 and 19 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly lacking enablement. The Examiner alleges that the instant specification, while being enabling for a method comprising contacting a compound with a TRAC1 polypeptide having the amino acid sequence of SEQ ID NO:1, does not reasonably provide enablement for a method comprising contacting a compound with any TRAC1 polypeptide or fragment thereof (*see,* pages 7-8 of the Office Action). To the extent the rejection is applicable to the amended set of claims, Applicants respectfully traverse the rejection.

Factors such as the amount of guidance presented in the specification and the presence of working examples must be considered to determine whether undue experimentation is required to practice the claimed invention. *See, e.g., Ex Parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Int. 1985) and *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). As described in *Wands*, "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction

in which the experimentation should proceed." *Wands*, USPQ2d at 1404, quoting *In re Jackson*, 217 USPQ 804 (Bd. Pat. App. & Int. 1982). Moreover, "[a] patent need not teach, and preferably omits, what is well known in the art." MPEP §2164.01, *citing In re Buchner*, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 221 USPQ 481, 489 (Fed. Cir. 1984).

As set forth in MPEP §2164.01, "the test of enablement is not whether any experimentation is necessary, but whether ... it is undue." Further, the "fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation" (citations omitted). Finally, claims reading on inoperative embodiments are enabled if the skilled artisan understands how to avoid inoperative embodiments. *See, e.g., In re Cook and Merigold*, 169 USPQ 299, 301 (C.C.P.A. 1971).

As discussed above, Applicants have amended the claims to recite a method for identifying a compound that modulates T lymphocyte activation by contacting the compound with a TRAC1 polypeptide comprising an amino acid sequence having at least about 90% identity to SEQ ID NO:1. Applicants assert that the level of identity required by the claims is intended to encompass other naturally-occurring variants and alleles of TRAC1 that have the same activity as a polypeptide having an amino acid sequence of SEQ ID NO:1, as well as closely related orthologs that can be used in the assays of the invention. In addition, this level of identity is intended to encompass variants engineered for ease of experimental manipulation, *e.g.*, variants that include amino acids that can be modified so that the polypeptide can be more easily purified.

Methods for determining percent identity are disclosed in the specification and are also well known to those of skill in molecular biology. These elements therefore provide adequate guidance for routine identification of the TRAC1 polypeptides of the claimed invention. In addition, the claims specify that the compound is identified by examining TRAC1-mediated modulation of T cell activation. Therefore, modulation of the TRAC1 polypeptide by the test compound is correlated with modulation of T cell activation. The level of skill in the biotechnological arts is considered to be very high. Therefore, given the high degree of identity

claimed in the present application (*i.e.*, at least about 90%) and the assays provided which allow one of skill in the art to test whether such a polypeptide has an altered T cell activation modulating activity, Applicants respectfully submit that undue experimentation is not required to practice the claimed invention.

Furthermore, some routine experimentation is tolerated by the enablement requirement. Again, given the high level of skill in the biotechnological arts, using the present invention the skilled practitioner would attempt to retain, not abolish, the activity of the polypeptide by suitable changes in its sequence. For example, the skilled practitioner would avoid inserting a run of 10 prolines in the sequence, which is known to alter the secondary structure of a polypeptide by creating bends or kinks. As described in the instant specification on page 16, lines 3-10, conservative amino acid substitutions are well known, where one amino acid is substituted by a chemically similar amino acid. The instant specification also lists a table of conservative amino acid substitutions (*see,* page 16, lines 11-16). Moreover, one of skill in the art would know how to routinely modify the polypeptide using a His tag or an epitope tag for purification, as well as using other know methodology.

In the present application, one of skill in the art has only to identify TRAC1 polypeptides, *e.g.*, using well-know sequence algorithms, which have at least about 90% identity to a conserved reference sequence. Although many such polypeptides are possible, one of skill in the art can readily determine, one by one, any particular TRAC1 polypeptide without undue experimentation. In addition, one of skill in the art can use the assays described in the instant specification to test T cell activation and easily determine if the polypeptide falls within the scope of the claims. Thus, in the present application the skilled artisan can readily, with only routine experimentation, make and test any particular claimed polypeptide.

Finally, Applicants respectfully bring to the Examiner's attention two recent decisions by the Board of Patent Appeals and Interferences: *Ex parte Sun,* Appeal No. 2003-1993 and *Ex parte Bandman*, Appeal No. 2004-2319. In both cases, the board found that claims directed to sequences with 80% or 95% identity to a reference sequence were enabled because the supporting specifications provided a single reference sequence and an assay for activity of

the encoded protein. Based on this analysis, allowance of the present claims that recite 90% identity to a reference sequence is appropriate.

The assays described in the instant specification, coupled with methodology well known to those of skill in the art, therefore demonstrate that screening for compounds that modulate TRAC1 polypeptide and thereby modulate T cell activation is routine. *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988).

In view of the foregoing remarks, Applicants respectfully request that the Examiner withdraw the enablement rejection under 35 U.S.C. § 112, first paragraph.

VII. REJECTION UNDER 35 U.S.C. § 102(b)

Claims 1-4, 6-10, 13-16, and 19 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Sitkovsky (U.S. Patent No. 5,180,662). To the extent the rejection is applicable to the amended set of claims, Applicants respectfully traverse the rejection.

A. Standard for anticipation

For a rejection of claims under § 102 to be properly founded, the Examiner must establish that a single prior art reference either expressly or inherently discloses each and every element of the claimed invention. *See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); and *Verdegaal Bros. V. Union Oil Co. Of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). In *Scripps Clinic & Research Found. v. Genentech, Inc.*, 18 USPQ2d 1001 (Fed. Cir. 1991), the Federal Circuit held that:

> Invalidity for anticipation requires that all of the elements and limitations of the claim are found with a single prior art reference. . . .There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention. *Id.* at 1010.

Anticipation can be found, therefore, only when a cited reference discloses all of the elements, features, or limitations of the presently claimed invention.

B. Standard for inherency

The MPEP states: "The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic." *See,* MPEP §2112 (emphasis in original), quoting *In re Rijckaert*, 28 USPQ2d 1955, 1957 (Fed.

Cir. 1993). Inherency "may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *See,* MPEP §2112, quoting *In re Robertson* 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999). Furthermore, "[i]n relying upon a theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *See,* MPEP §2112 (emphasis in original), quoting *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990).

C. Sitkovsky fails to explicitly or inherently teach that TRAC1 is involved in T cell activation

In the Office Action, the Examiner alleges that Sitkovsky teaches a method comprising contacting a compound with a TRAC1 polypeptide or a fragment thereof and determining the functional effect of the compound upon the TRAC1 polypeptide (*see,* page 11 of the Office Action). However, Sitkovsky only discloses a method for assaying cytotoxic T lymphocyte activation by measuring secreted granule-associated BLT esterase activity after incubating the cytotoxic T lymphocytes with activating stimuli. By contrast, the claims as amended are directed to a method for identifying a compound that modulates T lymphocyte activation by contacting the compound with a TRAC1 polypeptide comprising an amino acid sequence having at least about 90% identity to SEQ ID NO:1. In fact, Sitkovsky is not only silent regarding the role of TRAC1 in T cell activation, but also fails to teach or suggest a TRAC1 polypeptide having the structural characteristics (*i.e.,* at least about 90% identity to SEQ ID NO:1) of the claimed invention.

The Examiner appears to rely on a theory that Sitkovsky inherently teaches that T cell activation is modulated by TRAC1. However, the only reasoning to support this teaching is found in the instant specification. Prior to the present invention, it was not known that TRAC1 participated in T cell activation. In particular, Applicants respectfully assert that the instant specification provides the first demonstration that TRAC1is involved in T cell activation and T cell receptor (TCR) signaling, *e.g.,* by showing that mutant TRAC1 expression inhibits TCR-induced CD69 upregulation and calcium influx, identifying the function of TRAC1 as an E3

ubiquitin ligase, *etc.* Therefore, one of skill in the art would not have recognized Sitkovsky as inherently teaching a role of TRAC1 in T cell activation.

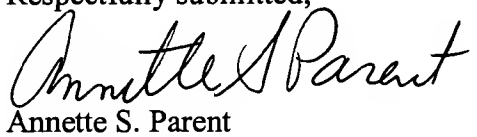
In view of the foregoing remarks, Applicants submit that Sitkovsky neither expressly nor inherently discloses each and every element of the claimed invention. Accordingly, Applicants respectfully request that the Examiner withdraw the 35 U.S.C. § 102(b) rejection.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



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